# Identification of neural and non-neural contributors to joint stiffness in upper motor neuron disease

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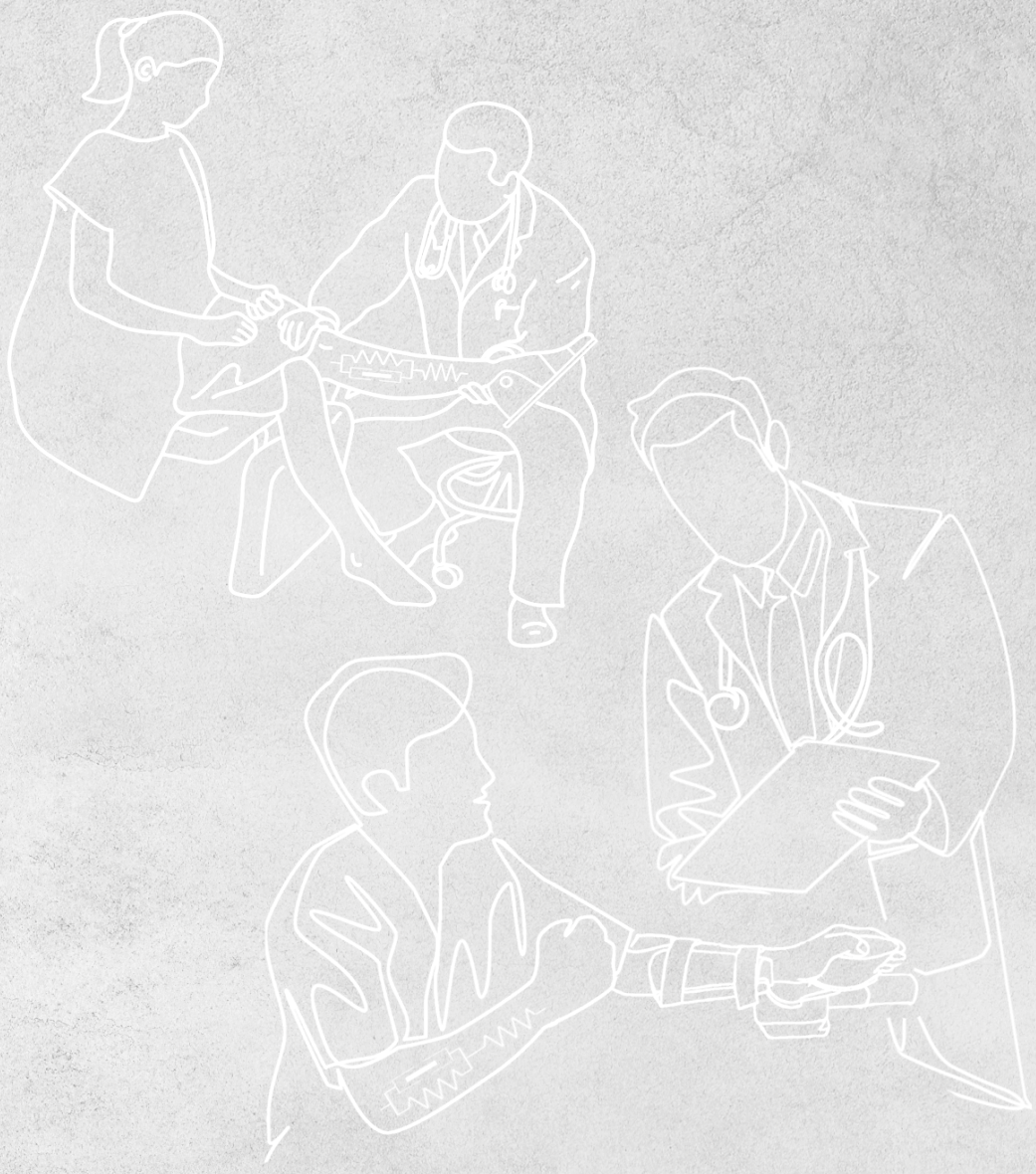
# CHAPTER 7

## Summary and general discussion



The aim of the studies in this thesis was to quantify neural reflexive and non-neural tissue contributors of ankle and wrist joint stiffness in patients with stroke and cerebral palsy using an instrumented electromyography (EMG) driven non-linear neuromuscular modeling approach. Underlying contributors of clinically observed increased joint stiffness, diminished range of motion and flexion deformity, i.e. a shift of joint rest angle, cannot be distinguished by current clinical tests like the Ashworth[1] and Tardieu scale[2;3], which are ordinal, subjective and of low resolution[4-6]. Quantification of underlying contributors is however important for understanding of underlying mechanisms of functional recovery and the effect of therapy on neural and non-neural components to diminish or eventually prevent these motor disorders. The clinical potential of the neuromuscular modeling approach was illustrated by the development over time of neural and non-neural contributors in the sub-acute phase post-stroke and by the effect of botulinum toxin A treatment on these contributors in chronic stroke patients.

## Main findings

In chapter 2 neural reflexive and non-neural tissue contributors of ankle joint stiffness were identified in patients with CP using an instrumented non-linear EMG-driven modeling approach[7]. Patients with CP showed a higher neural reflexive stiffness and peripheral tissue stiffness compared to healthy subjects. A large inter-subject variation was found for the ratio between reflexive stiffness and peripheral tissue stiffness showing the heterogeneity of the CP group. In patients with diminished range of motion, a high peripheral tissue stiffness was observed. The non-linear model[7] was refined and extended with parameters describing the passive and active force-length relationships such to estimate the optimal muscle length, slack muscle length and muscle stiffness, of the triceps surae and tibialis anterior (chapter 3). The added parameters enabled to identify muscle shortening and stiffening in patients with stroke. It was demonstrated that the model was internally valid and sensitive for knee angles. In chapter 4 the ankle model was translated to a wrist model. The model included an antagonistic pair of muscle elements reflecting the wrist flexor and extensor muscle groups. The model was valid and sensitive to demonstrate increased reflexive stiffness and peripheral tissue stiffness in chronic stroke patients compared to healthy controls and based on the smaller slack muscle length and smaller optimal muscle length it was suggested that flexor muscles were shortened

in patients with stroke[8]. Development of contributors over time was shown in a longitudinal study in the first 26 weeks post-stroke in chapter 5. Shortening of the wrist flexor muscles was demonstrated to occur as early as 4 to 5 weeks in a group of patients with poor prognosis for functional outcome at 26 weeks post-stroke and poor functional recovery of the upper extremity that clinically showed increased joint stiffness and wrist flexion deformity compared to patients with good recovery. Onset of neural reflexive stiffness in the poor recovery group occurred around week 12[9]. Temporal identification of components contributing to joint stiffness and flexion deformity post-stroke may prompt longitudinal interventional studies to further evaluate and eventually prevent the development of tissue shortening.



The effect of a common clinical intervention to reduce stiffness, increase dorsiflexion range of motion and counteract undesirable rest angle shifts, i.e. botulinum toxin A injection, on the neural reflexive and non-neural tissue contributors was observed in a longitudinal study in chronic stroke patients (chapter 6). Significant improvements in dorsal range of motion and shift of neutral angle, i.e. the rest angle of the joint at zero torque, were observed, which coincided with an estimated lengthening of the musculo-tendon complex of the triceps surae after botulinum toxin A treatment. Aforementioned improvements could be related to peripheral tissue stiffness, muscle slack length and soleus rest activity and could not be related to reflex activity. The results found in this study support evidence of the effect of botulinum toxin A on background muscle activity, i.e. muscle activation at rest, in post-stroke spasticity. These findings show the possibility to relate clinical observed changes, i.e. diminished range of motion and shift of rest angle, to its underlying neural and non-neural contributors and further in its pathophysiological changes which is required for understanding, diagnosis and follow-up. As the outcome parameters proved to be sensitive for treatment, these findings indicate that the modeling approach may be a powerful tool in treatment selection and quantifying the effect of treatment.

## Reflection

*Non-neural tissue changes precede neural reflexes changes*

In the EXPLICIT-trial (chapter 5) patients were followed 6 months post-stroke and stratified by prognosis for functional outcome at 26 weeks post-stroke, based on presence of finger extension and NIHSS, and recovery, based on ARAT[10]. This resulted in three groups: patients with good prognosis for functional recovery and good recovery, patients with poor prognosis and good recovery and patients with poor prognosis and poor recovery. In the group with poor recovery smaller wrist flexor slack lengths, representing muscle shortening, and increased peripheral tissue stiffness were observed to occur within 4-5 weeks after stroke followed by increased neural reflexive stiffness starting around 3 months.

Recovery after stroke varies with the nature and severity of the initial deficit after a cerebrovascular accident and is determined by unknown biological processes[11]. The mechanism of recovery of motor function on one side and development of shifted rest angle of the wrist on the other side are still poorly understood and mainly adhere to the first 8 weeks post-stroke[12;13]. A diminished neural input might result in disuse or immobilization; immobilized muscles in a shortened position adapt to their resting length and lose sarcomeres to develop force at their shortened length[14-18]. At comparable joint angles and compared to healthy muscles, the strain in spastic muscles is higher resulting in higher resistive muscle forces and a consequently higher joint stiffness due to the diminished number of sarcomeres in series[19]. Increased muscle strain in shortened muscle may potentially result in increased spindle response and consequently increased spinal reflex activity[16]. The development of increased background activation as a consequence of altered neural input may also result in hyperexcitability of reflexes[20;21]. There were no differences between the different groups in EMG magnitudes at rest suggesting that there was no difference in background muscle activation between the groups[9]. However, further substantiation requires a model that enables estimation of this neural contributor.

Non-neural tissue changes between the different recovery groups were observed within four weeks. An important focus in these first weeks might be to prevent the development of tissue changes in the acute and sub-acute phase post-stroke. Avoiding immobilization in a shortened position early after stroke might be an important aspect to prevent tissue changes. Possible treatments in the poor prognosis group may be to start immediately with physical therapy,

neuromuscular stimulation or splinting and casting to prevent flexion deformity. The instrumented non-linear neuromuscular modeling approach is a useful tool for follow-up to observe the neural and non-neural changes in time that correlate with the clinical observed changes, e.g. wrist flexion deformity, and it may be a useful tool to guide intervention at the right moment and at the right neuromuscular property.

*Botulinum toxin A lowers background muscle activation*

At 26 weeks post-stroke, patients with poor recovery showed increased neural reflexive torque and shortened and stiffened wrist flexor muscles resulting in increased peripheral tissue stiffness compared to stroke patients with good recovery[9]. This was in accordance with the results found in chronic stroke patients with an average of 30 (SD 27.6) months post-stroke (chapter 4). Here was found that patients with a modified Ashworth score of 1 or higher had increased reflexive stiffness of flexors, shortened flexor muscles and increased peripheral tissue stiffness compared to healthy subjects and patients with a modified Ashworth score of 0[8].



Botulinum toxin A treatment is a common clinical procedure to reduce joint stiffness, to increase dorsal range of motion and to correct shifted joint resting positions[22-29]. Botulinum toxin A blocks the release of acetylcholine from the nerve terminal, thereby uncoupling the excitation- contraction mechanism and thus reducing muscle (hyper)activity[26]. A lack of understanding the concept of spasticity in stroke may prevent optimal use of botulinum toxin A. It is important to know what the effect is of botulinum toxin A on the neural and non-neural components of joint stiffness and what the effect is on the association between these components, e.g. how will changes in the neural component interact with the changes of the non-neural components after stroke?[30]

After botulinum toxin A treatment, the dorsal range of motion increased and the neutral rest angle shifted (chapter 6). Baseline values and changes in peripheral tissue stiffness and triceps slack length were associated with the changes in dorsal range of motion and neutral angle and change in soleus EMG rest activity was associated with change in neutral angle. There were no associations found for changes in dorsal range of motion and neutral angle and changes in reflex activity. Large variation between patients was observed; not all of the patients showed improvements in outcome measures suggesting that there were responders and non-responders

to botulinum toxin A. Patients with high baseline peripheral tissue stiffness and/or small slack triceps muscle length seemed to benefit from botulinum toxin A. By examining patients on these properties, it may be possible to predict which patients might benefit from botulinum toxin A. Long term administration of botulinum toxin creates weakness and atrophy which may worsen motor function. Identifying the non-responders by low/normal peripheral tissue stiffness and/or normal slack length may help to prevent these undesirable effects and lowers medical expenses.

Following the administration of botulinum toxin A we were able to identify changes in the neural and non-neural contributors that were associated to increased dorsal range of motion and shifted neutral rest angle. This offers opportunities for further research: e.g. to study the effect of botulinum toxin A at an early stage after brain injury or to study the dose-response in botulinum toxin treatment[30].

Botulinum toxin is generally administered to reduce the neural reflexive component as spasticity is often defined according to the concept of Lance as a velocity dependent resistance to passive stretch[31]. In the current study, spasticity was explained by increased muscle activation at rest, i.e. background muscle activation[21]. Improvement in dorsal range of motion and neutral rest angle after botulinum toxin A can be explained by a decrease in an active contributor under rest conditions of the triceps surae muscles: botulinum toxin A may reduce background muscle activity so that the muscle relaxes and muscle length and range of motion increases. No associations in changes in dorsal range of motion and neutral angle were found for the neural reflexive components. Lowering background muscle activation by botulinum toxin might lower the increased reflex activity in contracted muscles[21], but this could not be confirmed in chapter 6 as the study was under passive conditions.

Background muscle activation could not be identified directly but may affect other parameters resulting in e.g. increased peripheral tissue stiffness and decreased slack muscle length, indicative for a decrease in pennation angle due to relaxation of muscle[32;33]. Considering the importance of background muscle activation as a neural contributor of joint stiffness, future model developments should be aimed at quantification of aforementioned contributor.

*Development of joint stiffness in stroke and cerebral palsy*

This thesis mainly focuses on stroke but application of the neuromuscular modeling approach was also shown in a group of patients with cerebral palsy. Both stroke and cerebral palsy are upper motor neuron diseases. Stroke appears mostly in adults in the developed brain; Cerebral palsy occurs in the fetal or neonatal developing brain[34]. Consequently, the posture and movement disorders may have a different sequel between the groups, which might be reflected in the neural and non-neural tissue distribution of joint stiffness. In patients with stroke we observed shortening of wrist flexor muscles around week 4 to 5 post-stroke and reflexive stiffness around week 12[9]. The development of contributors of joint stiffness over time in patients with cerebral palsy is not yet well described. From literature we learn that in cerebral palsy passive stiffness may increase over reflex activity with age[35] and that the range of dorsiflexion of the ankle joint decreased on average 19 degrees during the first 18 years of life[36]. From these two studies it is suggested that contribution of underlying components of joint stiffness in cerebral palsy changes over time and that variability in a group of adolescents is expected to be high. This latter was confirmed in our study in cerebral palsy by a large inter-subject variation for the ratio between triceps reflexive torque and peripheral tissue stiffness as we measured adolescents in a wide age range[37]. It would be interesting to study the change of underlying neural reflexive and non-neural tissue contributors of joint stiffness over time to learn more about the development of spasticity in cerebral palsy. As the contribution of neural reflexive and non-neural tissue stiffness might change over time, therapy in children with cerebral palsy needs to be evaluated whenever a new treatment strategy is considered.



## Future directions

*Assessment in clinical practice*

The presented instrumented EMG-driven non-linear neuromuscular modeling approach is applicable in patients showing a variable degree of flexion deformity, diminished range of motion and increased joint stiffness. Applicability was demonstrated in patients with stroke and cerebral palsy. The method is safe, as the range of motion is prevented by hard- and software stops, comfortable for the patient and does not require voluntary contraction. The method

resembles clinical tests, like the Ashworth and Tardieu tests, by the movement over the full range of motion. In contrast to linear system identification methods that apply small deviations of e.g. joint angle, performing movement over the full range of motion resembles functional movement more closely. Awareness is needed in patients with small range of motion: the movement velocity needs to be high enough to induce reflexes.

Assessment under passive conditions, as in the current study, does not resemble functional tasks that need voluntary muscle contraction, like walking. This requires assessment under active conditions.

Clinical applicability could be enhanced by reducing the preparation time which is two to three times longer than the measurements time, e.g. due to placing EMG electrodes on the muscles which is a precise task and necessary to quantify the neural and non-neural tissue parameters. Methods without EMG were developed, like the NeuroFlexor method, which showed good agreement with EMG-driven optimization on the overall neural and non-neural components[38;39], but lack the ability of precise quantification of parameters, e.g. slack muscle lengths, optimal muscle lengths and stiffness coefficients. This precise information is essential for insight in pathological mechanism in e.g. the sub-acute phase post-stroke and whether the muscle is shortened and/or stiffened which is of value in treatment selection. In case of e.g. a first exploration of overall joint stiffness in a patient, devices like the NeuroFlexor may be a good alternative.

*Neuromuscular model*

For administration of botulinum toxin A in e.g. the triceps surae, it can be of benefit to know whether the gastrocnemii are most affected or the soleus muscle. With the neuromuscular modeling approach it was possible to discriminate between groups of lumped muscle, e.g. plantar flexors and dorsiflexors, but not between individual muscles. An alternative method was presented for the ankle in chapter 3: by changing the knee angle, the contribution of the gastrocnemii muscles and soleus muscle was varying.

Muscle relaxation and activation, background muscle activation and muscle atrophy interfere with the muscle pennation angle[32;33;40]. This parameter was not included in the present model. Also, the elastic muscle tendon was not included. Including the Achilles tendon in the ankle

model did not significantly affect the model parameters in healthy subjects[41], but could be of value in patients with different phenotypes as Achilles tendon mechanical properties might be altered post-stroke[42]. Changes in pennation angle affect the passive and active force-length curves and thus interfere with the model parameters slack length, stiffness and optimal length. Thus it was not possible to determine whether an increased slack length in patients post-stroke may be caused by a reduced pennation angle due to muscle atrophy[40]. Additional measurements, like ultrasound, are required to study pennation angles as an additional input to the model.



## Clinical implications and recommendations

The results in this thesis are a step forward in answering "when" to treat stroke patients by performing longitudinal assessments. The EMG-driven neuromuscular modeling approach offers opportunity to gain more insight in the development of increased joint stiffness, diminished range of motion and rest angle shifts. This information is of value to prevent motor disorder developments in future.

The results in this thesis also gives direction to the question "how" to treat stroke patients, i.e. which treatment option is most effective in each individual patient, and is a step forward towards personalized treatment. Addressing effects of dose, injection site and technique and the potential to discriminate responders from non-responders are important subjects for further study considering the costs and the wide spread use of botulinum toxin A treatment. Quantification of neural and non-neural components is essential to diminish and eventually prevent motor disorders thereby improving activity of daily live and also quality of live in patients with stroke.

## References

(1) Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. *Practitioner* 1964;192:540-542.

(2) Tardieu C, Huet dlT, Bret MD, Tardieu G. Muscle hypoextensibility in children with cerebral palsy: I. Clinical and experimental observations. *Arch Phys Med Rehabil* 1982;63:97-102.

(3) Haugh AB, Pandyan AD, Johnson GR. A systematic review of the Tardieu Scale for the measurement of spasticity. *Disabil Rehabil* 2006;28:899-907.

(4) Lorentzen J, Grey MJ, Crone C, Mazevet D, Biering-Sorensen F, Nielsen JB. Distinguishing active from passive components of ankle plantar flexor stiffness in stroke, spinal cord injury and multiple sclerosis. *Clin Neurophysiol* 2010;121:1939-1951.

(5) Fleuren JF, Voerman GE, Erren-Wolters CV et al. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosurg Psychiatry* 2010;81:46-52.

(6) Meskers CG, de Groot JH, de Vlugt E, Schouten AC. NeuroControl of movement: system identification approach for clinical benefit. *Front Integr Neurosci* 2015;9:48.

(7) de Vlugt E, de Groot JH, Schenkeveld KE, Arendzen JH, van der Helm FC, Meskers CG. The relation between neuromechanical parameters and Ashworth score in stroke patients. *J Neuroeng Rehabil* 2010;7:35.

(8) de Gooijer-van de Groep K, de Vlugt E., van der Krogt HJ et al. Estimation of tissue stiffness, reflex activity, optimal muscle length and slack length in stroke patients using an electromyography driven antagonistic wrist model. *Clin Biomech* 2016;35:93-101.

(9) de Gooijer-van de Groep KL, de Groot JH, van der Krogt H, de Vlugt E, Arendzen JH, Meskers CGM. Early Shortening of Wrist Flexor Muscles Coincides With Poor Recovery After Stroke. *Neurorehabil Neural Repair* 2018;1545968318779731.

(10) Kwakkel G, Meskers CG, van Wegen EE et al. Impact of early applied upper limb stimulation: the EXPLICIT-stroke programme design. *BMC Neurol* 2008;8:49.

(11) Dobkin BH. Clinical practice. Rehabilitation after stroke. *N Engl J Med* 2005;352:1677-1684.

(12) Kwakkel G, Kollen B. Predicting improvement in the upper paretic limb after stroke: a longitudinal prospective study. *Restor Neurol Neurosci* 2007;25:453-460.

(13) van Kordelaar J, van Wegen E, Kwakkel G. Impact of time on quality of motor control of the paretic upper limb after stroke. *Arch Phys Med Rehabil* 2014;95:338-344.

(14) Tabary JC, Tabary C, Tardieu C, Tardieu G, Goldspink G. Physiological and structural changes in the cat's soleus muscle due to immobilization at different lengths by plaster casts. *J Physiol* 1972;224:231-244.

(15) Williams PE, Goldspink G. Changes in sarcomere length and physiological properties in immobilized muscle. *J Anat* 1978;127:459-468.

(16) Gracies JM. Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. *Muscle Nerve* 2005;31:535-551.

(17) Kelleher AR, Gordon BS, Kimball SR, Jefferson LS. Changes in REDD1, REDD2, and atrogene mRNA expression are prevented in skeletal muscle fixed in a stretched position during hindlimb immobilization. *Physiol Rep* 2014;2:e00246.

(18) Wisdom KM, Delp SL, Kuhl E. Use it or lose it: multiscale skeletal muscle adaptation to mechanical stimuli. *Biomech Model Mechanobiol* 2015;14:195-215.

(19) Lieber RL, Friden J. Spasticity causes a fundamental rearrangement of muscle-joint interaction. *Muscle Nerve* 2002;25:265-270.

(20) Denny-Brown D. Chapter XII. The extrapyramidal cortical system. *The Cerebral Control of Movement*. Liverpool: University Press; 1966;173.

(21) Burne JA, Carleton VL, O'Dwyer NJ. The spasticity paradox: movement disorder or disorder of resting limbs? *J Neurol Neurosurg Psychiatry* 2005;76:47-54.

(22) Brashear A, Gordon MF, Elovic E et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002;347:395-400.

(23) Sheean G. Botulinum toxin treatment of adult spasticity. *Expert Rev Neurother* 2003;3:773-785.

(24) Sheean G. Botulinum toxin should be first-line treatment for poststroke spasticity. *J Neurol Neurosurg Psychiatry* 2009;80:359.

(25) Ward AB. Spasticity treatment with botulinum toxins. *J Neural Transm (Vienna )* 2008;115:607-616.

(26) Simpson DM, Gracies JM, Graham HK et al. Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;70:1691-1698.

(27) Rosales RL, Chua-Yap AS. Evidence-based systematic review on the efficacy and safety of botulinum toxin-A therapy in post-stroke spasticity. *J Neural Transm (Vienna )* 2008;115:617-623.

(28) Rosales RL, Efendy F, Teleg ES et al. Botulinum toxin as early intervention for spasticity after stroke or non-progressive brain lesion: A meta-analysis. *J Neurol Sci* 2016;371:6-14.

(29) Wu T, Li JH, Song HX, Dong Y. Effectiveness of Botulinum Toxin for Lower Limbs Spasticity after Stroke: A Systematic Review and Meta-Analysis. *Top Stroke Rehabil* 2016;23:217-223.

(30) Kwakkel G, Meskers CG. Botulinum toxin A for upper limb spasticity. *Lancet Neurol* 2015.

(31) Lance JW. Spasticity: Disordered Motor Control. In: Feldman R, Young R, Koella W, eds. *Symposium Synopsis*. C: Year Book Medical Publishers; 1980;485-495.

(32) Tok F, Ozcakar L, Safaz I, Alaca R. Effects of botulinum toxin-A on the muscle architecture of stroke patients: the first ultrasonographic study. *J Rehabil Med* 2011;43:1016-1019.

(33) Kawano A, Yanagizono T, Kadouchi I, Umezaki T, Chosa E. Ultrasonographic evaluation of changes in the muscle architecture of the gastrocnemius with botulinum toxin treatment for lower extremity spasticity in children with cerebral palsy. *J Orthop Sci* 2018;23:389-393.

(34) Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG, Erez O. Cerebral Palsy-Trends in Epidemiology and Recent Development in Prenatal Mechanisms of Disease, Treatment, and Prevention. *Front Pediatr* 2017;5:21.

(35) Pierce SR, Prosser LA, Lauer RT. Relationship between age and spasticity in children with diplegic cerebral palsy. *Arch Phys Med Rehabil* 2010;91:448-451.

(36) Hagglund G, Wagner P. Spasticity of the gastrosoleus muscle is related to the development of reduced passive dorsiflexion of the ankle in children with cerebral palsy. *Acta Orthop* 2011;82:744-748.

(37) de Gooijer-van de Groep KL, de Vlugt E, de Groot JH et al. Differentiation between non-neural and neural contributors to ankle joint stiffness in cerebral palsy. *J Neuroeng Rehabil* 2013;10:81.

(38) Gaverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson AC. Test-retest and inter-rater reliability of a method to measure wrist and finger spasticity. *J Rehabil Med* 2013;45:630-636.

(39) Scholte L. *Validation of the NeuroFlexor method for obtaining the neural and intrinsic component of wrist hyper-resistance post stroke*. TU Delft, The Netherlands; 2018.

(40) Ramsay JW, Buchanan TS, Higginson JS. Differences in Plantar Flexor Fascicle Length and Pennation Angle between Healthy and Poststroke Individuals and Implications for Poststroke Plantar Flexor Force Contributions. *Stroke Res Treat* 2014;2014:919486.

(41) van de Poll KD. *Estimating ankle muscle parameters.* TU Delft, The Netherlands; 2016.

(42) Zhao H, Ren Y, Wu YN, Liu SQ, Zhang LQ. Ultrasonic evaluations of Achilles tendon mechanical properties poststroke. *J Appl Physiol* 2009;106:843-849.